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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/087,473	03/01/2002	Melissa K. Carpenter	090/003C	1663

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EXAMINER	
TON, THAIAN N	
ART UNIT	**PAPER NUMBER**
1632	

DATE MAILED: 02/10/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/087,473	CARPENTER ET AL	
	Examiner	Art Unit	
	Thaian N. Ton	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 November 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,4-6 and 30-32* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,4-6 and 30-32* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 11/18/05 has been entered.

Applicants' Amendment and Remarks, filed 11/18/05, have been entered and considered. Claims 2, 9-11, 17, 18 and 29 are cancelled; claim 1 is amended; claims 1, 4-6, 30-32 are pending and under current examination.

Specification

The prior objection to the disclosure is withdrawn in view of Applicants' amendment to remove the embedded hyperlink.

Response to Arguments

The prior rejections of 1-2, 4-6, 9-11, 17-18, 30-32 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement (new matter) and under 35 U.S.C. 112, first paragraph, for enablement, are withdrawn in view of Applicants' amendment to the claims which no longer recite that at least 2% of the cells express tyrosine hydroxylase.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not

patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., In re Berg, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); In re Goodman, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); In re Longi, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); In re Van Ornum, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); In re Vogel, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and In re Thorington, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1, 4-6, 30-32 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 34-46 of copending Application No. 09/888,309. Although the conflicting claims are not identical, they are not patentably distinct from each other because they are both directed to producing differentiated cells from undifferentiated human ES cells. The instant claims are directed to a method of producing a population of cells comprising neurons that express tyrosine hydroxylase, the method comprising plating and culturing undifferentiated hES cells on a solid surface, so that they differentiate without forming embryoid bodies, culturing the plated cells in a medium containing a TGF-β superfamily antagonist; harvesting a population of cells form the solid surface, wherein the population of cells comprises neurons that express tyrosine hydroxylase. Particular embodiments of the instant claims limit the antagonist to noggin or follistatin, and that the medium further contains a neurotrphoin, which is NT-3 or BDNF. The '309 claims recite a system for producing differentiated cells from hES cells consisting of hES cells and a second population of cells, which are progeny of the hES cells, in a medium containing one or more added TGF-β superfamily antagonists, and specifically teach that this cell

population is produced by culturing the hES cells in a medium that contains either noggin or follistatin (claims 37-38), and that the differentiated cells comprise at least 10% neural cells identifiable by the criteria that they express both microtubule associated protein 2 and tyrosine hydroxylase (claim 35), wherein the medium further contains a neurotrophin which is neurotrophin 3 or BDNF (claims 39-40). The '309 claims further encompass obtaining the differentiated cells by plating hES cells on a solid surface without forming embryoid bodies (claim 45). Therefore, given that that '309 claims recite the same factors and conditions that would be used in order to produce differentiated, neural cells that express tyroxsine hydroxylase, the render the instant claims obvious.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 4-6, 30-32 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for method of producing a population of cells that comprise neurons that express tyrosine hydroxylase by plating and culturing undifferentiated human ES cells on a solid surface so that they differentiate without forming embryoid bodies, culturing the plated cells in a medium that contains *noggin and follistatin*, harvesting a population of cells from the solid surface, wherein the cells comprise neurons that express tyrosine hydroxylase, does not reasonably provide enablement for the breadth of the claims, utilizing any TGF-β superfamily antagonist. The specification does not enable any

person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Enablement is considered in view of the Wands factors (MPEP 2164.01(A)). These include: nature of the invention, breadth of the claims, guidance of the specification, the existence of working examples, state of the art, predictability of the art and the amount of experimentation necessary. All of the Wands factors have been considered with regard to the instant claims, with the most relevant factors discussed below.

The claims, as instantly amended, are directed to methods for producing a population of cells comprising neurons that express tyrosine hydroxylase, the method comprising plating and culturing undifferentiated hES cells on a solid surface, so that they differentiate without forming embryoid bodies, culturing the plated cells in a medium containing a TGF-β superfamily antagonist; harvesting a population of cells form the solid surface, wherein the population of cells comprises neurons that express tyrosine hydroxylase.

Applicants' Arguments. The prior Office action (mailed 7/5/05) stated that only using follistatin or noggin would arrive at the claimed invention (neurons), and that this argument is based upon the contention that Test Group 4 was unable to provide any noticeable percentage of TH positive cells. Applicants traverse this argument because they state that Group 4 only relates to agonists, not antagonists. With regard to rejections presented in the prior Office action, Applicants have now amended the claims such they do not recite that the population of cells contain 2% nneural cells. See page 7 of the Response.

Response to Arguments. These arguments are found persuasive with regard to the amendment to the claims, which no longer require a particular percentage of resultant cells. The Examiner agrees that Test Group 4 recites agonists, not antagonists of TGF-β superfamily proteins. However, the breadth of the claims, encompassing any TGF-β superfamily antagonist in order to arrive at the claimed

invention is not enabling. The state of the art of directing differentiation of hES cells is found to be unpredictable (see Du *et al.*, cited in the Office action mailed 12/17/04), who clearly show that directing differentiation of ES cells to neural cells is inefficient, and that usually this neural differentiation requires aggregation of the cells. The working examples in the specification provide guidance with regard to using specific TGF-β superfamily antagonists, noggin and follistatin. In particular, Group 5 specifically recite noggin, and follistatin. See Table 3. Table 4 provides the results from these experiments, and it is noted that only those treatments which contain Test Group 5 (*i.e.,* noggin and follistatin) are able to produce any cells with TH positive staining. See Treatments B, D, and F. There is no teaching, guidance, or evidence of record to show that utilizing any other TGF-β superfamily antagonists that would result in the production TH positive neurons, as required by the claims. TGF-β superfamily genes encode proteins with extremely diverse functions, and it would not be predictable that the broad range of antagonists of these proteins would function to direct differentiation of hES cells to neurons, as required by the claims. For example, Massagué (**Cell**, 49: 437-438 (1987)) teach that TGF-β superfamily proteins elicit a large variety of cellular responses (for example, TGF-β1 and TGF-β2 strongly inhibit proliferation of normal and certain tumor-derived epithelial cell lines, see p. 437, 1st column, last ¶) and that TGF-β proteins are present in various tissues, such as cartilage, osteocytes, thymus, bone marrow, etc. (see p. 437, 2nd column, 2nd ¶). Although TGF-β is often found in tissues that are differentiating, the tissues are varied, as are the functions. For example, MIS is found exclusively in the mammalian testes and causes regression of the Mullerian ducts during development, which TGF-β does not mimic; additionally, inhibins and activins control the expression of differentiated functiosn in the ovarian-pituitary FSH and accumulation of estrogen in ovarian granulose cells (see p. 438, 1st column, ¶ 2-3). Thus, because TGF-β superfamily genes function in varied pathways, have different effects upon different and varied

tissues, it would not be predictable to use any particular antagonist, other the exemplified noggin and follistatin, in order to produce neuron that express TH.

Accordingly, in view of the state of the art with regard to the production of a particular cell type from hES cells, the varied expression and function of TGF-β superfamily genes and their encoded peptides, and the working examples in the specification, which only provide guidance for using noggin and follistatin to produce neurons, it would have required undue experimentation for one of ordinary skill in the art to make and use the claimed invention, as instantly claimed, using any TGF-β superfamily antagonist.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claim 1, 4-6, 30-32 rejected under 35 U.S.C. 103(a) as being unpatentable over Thomson *et al.* (**Science**, 282:1145-1147 (1998), Document BC of Applicants'

IDS, filed 4/26/02) in view of Weiss and in further view of Melton *et al.* (Weiss and Melton cited in the Office action mailed 5/4/04)

The claims are directed to methods for producing a population of cells comprising neurons that express tyrosine hydroxylase (TH), by plating and culturing undifferentiated hES cells on a solid surface so that they differentiate without forming embryoid bodies, culturing the cells in a medium containing a TGF-β superfamily antagonist and harvesting a population of neurons that express TH. Specific embodiments are directed to plating the cells on a solid surface without extracellular matrix (claim 4); the solid surface comprises a polycation which is either polyornithine or polylysine (claims 4-6); the TGF-β superfamily antagonist is either noggin or follistatin (claim 30); the medium further contains a neurotrophin which can be either neurotrophin-3 (NT-3) or brain derived neurotrophic factor (BDNF).

Claim Interpretation. The claims require that the differentiated cell population comprise neurons. Thus, art that provides reasonable expectation of producing at least one neuron from an undifferentiated human ES cell fulfills this limitation.

Thomson *et al.* teach the generation of human ES cells from human blastocysts. They teach that the ES cells can generate cells from all three germ layers, including neural tissue and ganglia (see Abstract and page 1146, col. 1, 2nd full ¶). Thomson does not teach the replating of the cells on a solid surface that is coated with a polycation, and harvesting the differentiated cells from the solid surface, or culturing the ES cells in a medium that contains a TGF-β superfamily antagonist, or culturing the cells in a medium that contains a specific neurotrophin (such as BDNF or NT-3)

However, prior to the time the claimed invention was made, Weiss teach the *in vitro* proliferation and differentiation of neural stem cells. They teach that stem cells give rise to progenitor cells which give rise to proliferating cells, such as

neuroblasts, glioblasts, etc. See col. 1, lines 63-67. They teach methods for the *in vitro* differentiation of neural stem cells and stem cell progeny by isolating stem cells from a mammal, exposing the cell to a medium containing a growth factor to induce the cell to proliferate and differentiate. They teach that in the presence of proliferation-inducing growth factor(s), the stem cell divides and gives rise to a sphere of undifferentiated cells, wherein when the cells are dissociated and plated as single cells on a non-adhesive substrate and under conditions that allow differentiation, the cells differentiation into neurons, astrocytes and oligodendrocytes. See col. 11, lines 39-50. In particular, the dissociated neural cells can be induced to differentiate by culturing the cells on a substrate such as poly-ornithine treated glass or plastic to differentiate into neurons and glial cells. See col. 18, lines 30-55. Furthermore, exogenous growth factors may be added to direct differentiation of the stem cells, for example, BDNF and NT-3 (col. 2, lines 25-39). They further teach that utilizing these methods they found expression of tyrosine hydroxylase in the resultant neural cells (see col. 56, Table 1).

Thomson and Weiss do not teach that the differentiation medium used to culture the cells contains noggin or follistatin. However, Melton teaches methods for inducing neuronal cell differentiation. Particularly, they teach that stem cells can be induced to differentiate into a committed progenitor cell, or a terminally differentiated neuronal cell by culturing with an agent that antagonizes the biological action of activin, such as follistatin, and a second agent which is a neurotrophic factor that enhances a particular differentiation fate of the cell, such as noggin. See col. 9, lines 8-30 and col. 9-10, bridging ¶ and claims 1, 4 and 13.

Accordingly, in view of the combined teachings of Thomson, Weiss and Melton, it would have been obvious for one of ordinary skill in the art at the time the claimed invention was made, to culture stem cells, such as those taught by Thomson to differentiate in a culture medium that contains follistatin or noggin, as taught by Weiss and Melton, to produce neurons that express TH, with a reasonable

expectation of success. One of ordinary skill in the art would have been motivated to do so because the presence of factors such as follistatin and noggin can be employed to maintain the integrity of a culture of terminally-differentiated neuronal cells by preventing loss of differentiation as taught by Melton (see col. 9, lines 8-13). Furthermore, as the claims only require that the resultant population of cells comprise neurons. Thus, one of ordinary skill would have a reasonable expectation of success, given the teachings of Thomson, Weiss and Melton, to produce a TH-expressing neuron from an human ES cell.

Thus, the claimed invention, as a whole, is clearly *prima facie* obvious in the absence of evidence to the contrary.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Thaian N. Ton whose telephone number is (571) 272-0736. The Examiner can normally be reached on Monday through Thursday from 7:00 to 5:00 (Eastern Standard Time). Should the Examiner be unavailable, inquiries should be directed to Ram Shukla, SPE of Art Unit 1632, at (571) 272-0735. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the Official Fax at (571) 273-8300. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989).

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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